
THE WELLCOME TRUST
Institute
of Cancer and
Developmental
Biology
CANCER RESEARCH CAMPAIGN
UNIVERSITY OF CAMBRIDGE
1995

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ANNUAL REPORT 1994



University of Cambridge

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Front Cover Photograph:

Cyclin B1 distribution in cells
Human fibroblasts stained for cyclin B1 (green), DNA (blue) and the Golgi apparatus (yellow)

Photograph by Mark Jackman (see page 29)

FOREWORD BY THE CHAIRMAN

HISTORICAL BACKGROUND The institute was founded to promote research in the areas of Developmental Biology and Cancer Biology. It is an assemblage of independent research groups located in one building designed to promote as much interaction as possible. Developmental and cancer biology are complementary since developmental biology is concerned with how cells come to acquire and maintain their normal function; cancer is a result of a cell breaking loose from its correct controls and becoming abnormal . Both areas require a detailed knowledge of intracellular processes, which need to be analyzed at the cellular and molecular levels. These research areas are complementary at the scientific and technical levels. To understand what goes wrong when a cell becomes cancerous requires a knowledge of the processes which ensure correct cell function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques which no one person can master, such as gene cloning, antibody preparation, cell culture, and embryological manipulation. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another.





PRESENT STATUS Our institute is now well established, with over 150 total personnel. We consist of 16 independent research groups, containing postdoctoral scientists, visitors, research assistants, and a total of 36 graduate students. Each group is affiliated to one of the University Departments. The teaching we do and our lists of publications are credited to our affiliated departments, and we have access to their workshops and equipment.

THE INSTITUTE IN 1994 In the course of this year, Jordan Raff has established his group, and will be building it up progressively. We hope to add two or three new Wellcome-funded groups in the course of the next few years.

Earlier this year, Jonathon Pines received the 32nd Colworth Medal of the Biochemical Society, which is awarded annually to 'the most promising young biochemist'. The medal was in recognition of his work in isolating the first human cyclins, and in showing that their amounts are controlled both at the level of transcription, and of destruction at mitosis. Dr Pines developed these studies to demonstrate that different cyclins are able to control distinct processes in the cell cycle because cyclins are localised to particular subcellular structures such as the cytoskeleton and the mitotic apparatus.

We are very pleased that Dr Martin Evans was awarded an *ad hominem* Professorship in Mammalian Genetics in October, and two of our other members have been elected to tenure Lectureships in this University. Dr Anne Ferguson-Smith has recently taken up her appointment in the department of Anatomy, and Dr Bill Colledge will join the Physiological Laboratory in April 1995.

During part of 1994, Dr Pere Alberch, Director of the National Museum of Natural History in Madrid, spent some months in the group of Dr Michael Akam and gave a popular course of lectures in the institute on Development and Evolution.







Last year's retreat proved to be a great success and was consequently repeated this year. Organised jointly by Dr Tony Kouzarides and Dr Nick Brown, the event provides an opportunity for two days of intense scientific interaction, lightened by a little competitive sport.

In 1991, Dr Tony Kouzarides negotiated the establishment of our Du Pont/NEN/ Boehringer Lecture Programme, which has enabled us, this year, to host some 27 outside research lectures, many given by overseas visitors.

We invited two of our younger members to organise the Developmental Biology lunchtime seminars, held in the Department of Genetics, a series that has been running for some years in Cambridge, and which annually attracts a wide audience from the local community. The current series is being organised by Dr Greta Mathews and Matthew Weston.

As part of our graduate student programme, Dr Daniel St Johnston organises a series of talks given by graduate students on Wednesday lunchtimes during term, while on behalf of Cambridge's very active *Drosophila* community. Dr Nick Brown organises a series of Monday evening research talks in the institute. In a wider context, CRC grantees support fundraising by talking about their work to local committees and to members of the public, some of whom will have financed items of equipment after a particular fundraising event.

John Gurdon.

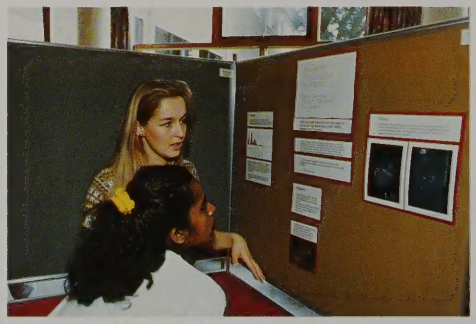
JOHN GURDON
CHAIRMAN

One of the most important things to encourage in a major institute is interaction between groups. To help achieve this the laboratory space within the building is specifically organised in such a way as to promote meetings and discussion. This has a beneficial effect not only on the interchange of scientific ideas but also on the social environment within the institute and on its wider reputation. As a consequence we have welcomed many new members during the past year, with an increase in active research grants of more than 30%, the research grant expenditure reaching 2.8 million pounds in the Academic Year 1993/94.

Within the next two years we should be able to spread our wings a little further, when the new extensions to the Institute, funded by the Wellcome Trust and the Cancer Research Campaign, will be completed. Primarily providing extra laboratory space, the extension will include additional seminar room space facilitating group meetings and the increasing number of lectures/seminars hosted by the institute.

We encourage everyone in the institute to feel part of a team. To help technicians and support staff to understand more about the research being undertaken throughout the building we have instituted a series of informal talks by Group Leaders entitled "Cancer and Developmental Biology made simple." Complementing these is a series run by the





research support staff themselves on the laboratory techniques used by the various groups. We also host talks, open to all staff of the University, which help to explain how the University's Central Administration is structured and functions in relation to the funding and support of Science.

Understanding and collaborating in the scientific research of the institute is not the only way of encouraging good relations between

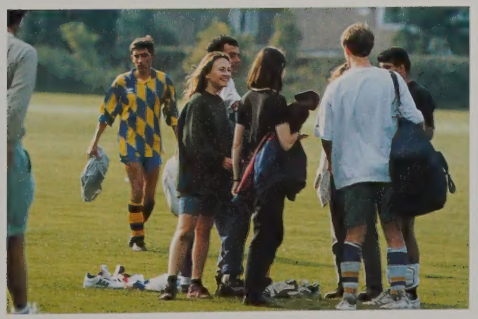
and within groups: we have a splendid large, sunny tea room where anyone can go during the day to drink tea/coffee etc., or have lunch while meeting up with friends and colleagues who work in different parts of the building. The legendary prowess of our resident football team, the "Wellcome Wanderers", will be tested in a full season of matches against teams from both other University departments and local clubs. During the summer many Institute members enjoy rounders matches against other departments; and, not all of us being sports fans,we regularly arrange theatre trips. Ideas for further social activities are always welcomed and we look forward to a particularly successful year in 1995.



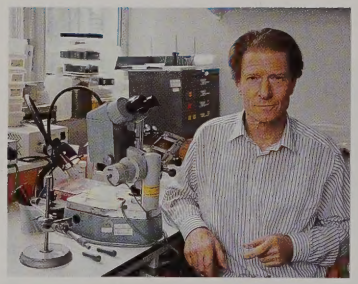




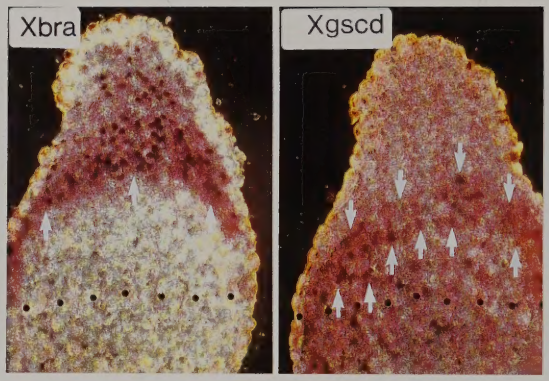




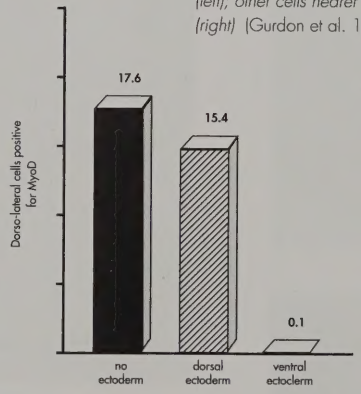
JOHN GURDON



GILLES CARNAC
AGNES CHAN
DEVANAND CREASE
NIGEL GARRETT
DANIEL MAHONY
NATASHA MCDOWELL
ANDREW MITCHELL
KEN RYAN
FIONA STENNARD
ELIZABETH TWEED



Sections through directional conjugates. Cells injected with activin mRNA are below the dotted line. Some of the cells above the line respond to activin signalling by expressing the gene Xbrachyury *(left); other cells nearer the signalling source express* Xgoosecoid *(right)* (Gurdon et al. 1994, Ref. below)



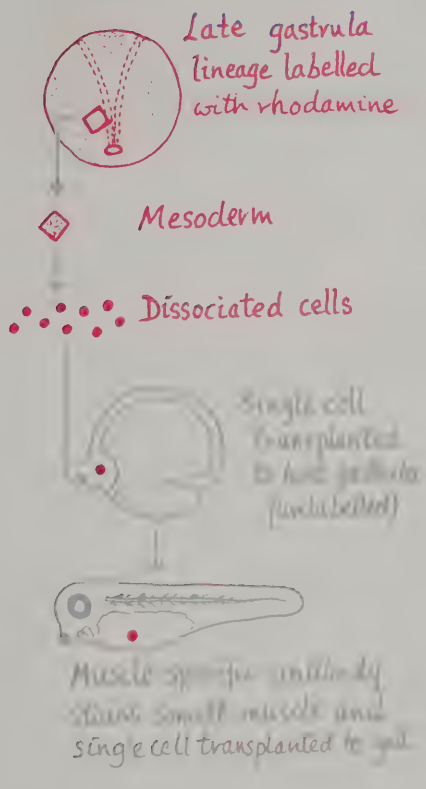
Dorso-lateral early gastrula cells activate muscle genes (XMyoD) if cultured in a group. Ventral (but not dorsal) ectoderm of a gastrula is strongly inhibitory. A community effect and a counteracting inhibitory influence seem to promote uniformity within muscle tissue, and demarcation from other neighbouring tissues. (Ref. 56)

GURDON, J.B., HARGER, P., MITCHELL, A. and LEMAIRE, P. 1994. Activin signalling and response to a morphogen gradient. **Nature 371**, 487-492.

GURDON, J.B., TILLER, E., ROBERTS, J., and KATO, K. 1993. A community effect in muscle development. **Current Biology 3**, 1-11.

For further publications, see nos. 49,50,54,56,65,66,99, page 47ff.

MECHANISMS OF CELL DIFFERENTIATION IN EARLY AMPHIBIAN DEVELOPMENT



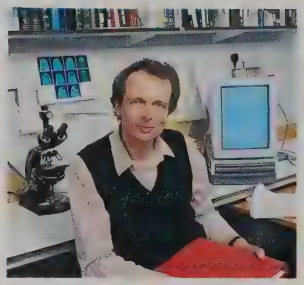
Single cell transplantation

How do differences between cells first arise in early embryos? In the Vertebrates, much the most important mechanism leading to cell differences is interactions between cells. We are analysing this process in Amphibia: a few hours after fertilization, cells at one end of the embryo induce those at the other to become muscle, which is one of the first differentiated cell-types to be formed in embryos.

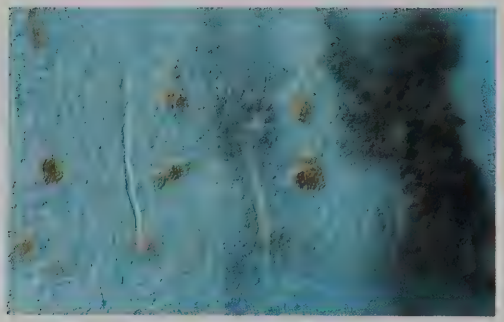
A particularly important aspect of this mesoderm-forming induction is that cells seem to respond to different concentrations of a signalling molecule, such as activin, to form mesodermal cell-types like muscle, notochord, etc. We have obtained direct evidence for the operation of morphogen gradient by using directional conjugates in which a concentration gradient of activin spreads from a source through a population of responsive cells. The choice of cells which respond to the gradient by expressing the genes *Xbrachyury* and *Xgoosecoid* is determined by their distance from the source, that is by the concentration of morphogen that they receive.

The mesoderm-forming induction is immediately followed in *Xenopus* by community effects in the notochord and muscle and by an inhibitory influence of ventral ectoderm - these processes are believed to refine early responses to a morphogen gradient by increasing uniformity within, and demarcation between, mesodermal cell-types. We are actively engaged in trying to identify new genes for these various mesodermal activities, using a functional screen of subtracted cDNA libraries.

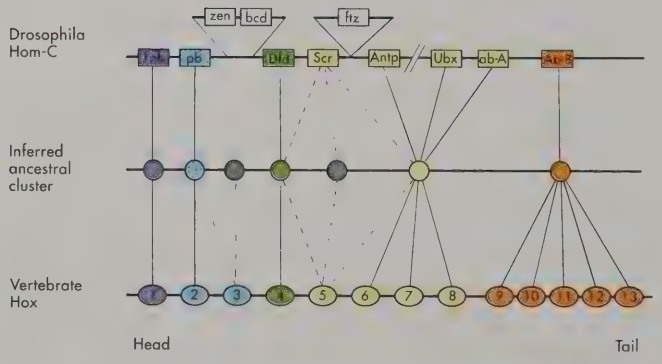
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KAREN HO
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LOUISE SMITH
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A single Hox gene can specify different fates for several different segments. In this case, the expression of Ultrabithorax modifies the development of most cells in parasegment 6 (heavy grey stain) but only a subset of cells in parasegment 5.



Comparison of insect and vertebrate Hox clusters

CASTELLI-GAIR, J., GREIG, S., MICKLEM, G. and AKAM, M. 1994. Dissecting the temporal requirements for homeotic gene function. **Development 120**, 1983-1995.

DAWES, R., DAWSON, I., FALCIANI, F., TEAR, G. and AKAM, M. 1994. Dax, a Locust Hox gene related to *fushi-tarazu* but showing no pair-rule expression. **Development 120**, 1561-1572.

For further publications, see nos. 1,2,3,4,5,8,29,58, page 47ff.

HOMEOTIC GENES AND SEGMENT PATTERNING IN INSECTS AND CRUSTACEA

Some of the mechanisms that generate pattern during embryogenesis are ancient and conserved. A striking example is the use of the same family of genes, the Hox genes, to define position from front to back in the embryos of flies and man. In other respects, each individual species is specialised. For example, some processes that transmit maternal information to the developing embryo in *Drosophila* appear to be without parallel, even in other insects.

Our work focuses on the Hox genes. To study how the products of the Hox genes affect cell fate, we are modifying the structure and regulation of Hox proteins *in vivo*. Our recent work has focused on the importance of temporal and spatial regulation of the Hox genes for the proper specification of segment identity.

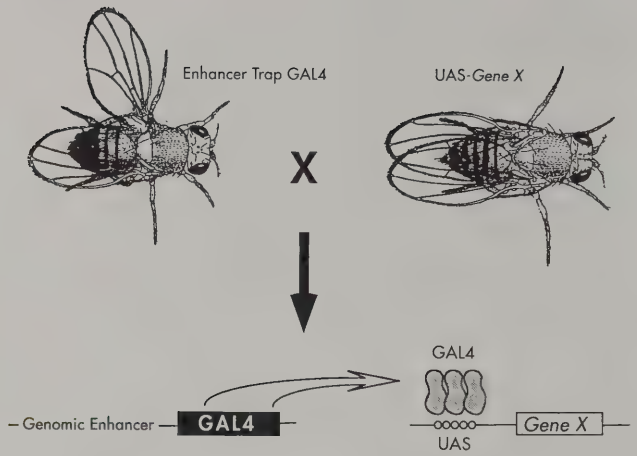
In *Drosophila*, a subset of the Hox cluster genes have acquired roles in early development that are without parallel in vertebrates. These "atypical" Hox genes - *fushi-tarazu*, *bicoid* and *zen*, appear to have acquired new roles in early embryonic development. With both conserved and divergent members, the Hox cluster provides an interesting model to study how the developmental role of genes may change during evolution. We are isolating Hox genes from diverse insects and crustaceans, determining when and where they are expressed, and investigating their function, both *in situ* and in transgenic *Drosophila*.



ANDREA BRAND



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The GAL4 activation system for targeted gene expression



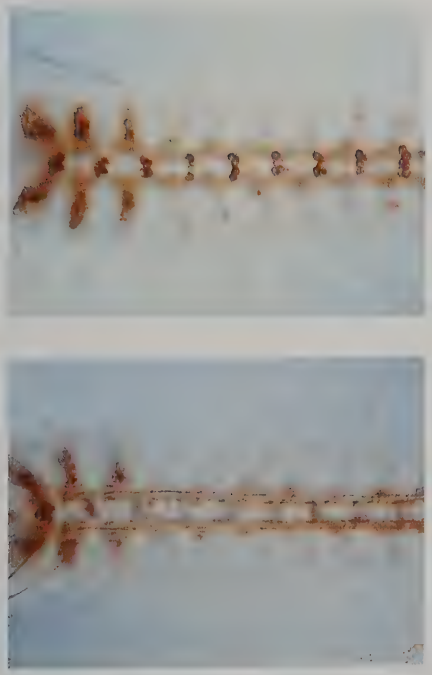
GAL4-directed expression of ß-galactosidase in cells along the ventral midline (stained blue). Axons are labelled in brown.

BRAND, A.H. and PERRIMON, N. 1993. Targeted gene expression as a means of altering cell fates and generating dominant phenotypes. **Development 118**, 401-415.

BRAND, A.H and PERRIMON, N. 1994. Raf acts downstream of the EGF receptor to determine dorsoventral polarity during *Drosophila* oogenesis. **Genes Dev. 8**, 629-639.

For further publications see nos. 10,90, page 47ff.

THE DEVELOPMENT OF THE EMBRYONIC NERVOUS SYSTEM IN *DROSOPHILA*



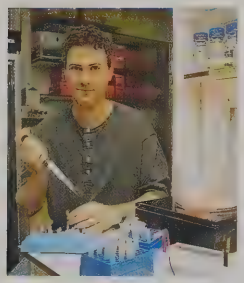
An embryo expressing a tau-ß galactosidase fusion protein in the central nervous system. Two focal planes are shown.

To generate a functional nervous system requires the production of a large number of neurons, each with a specific identity. Each neuron must migrate to a characteristic position within the nerve cord from which it can extend an axon towards, and synapse with, an appropriate target cell. The expression of segmentation genes is known to be a necessary step in establishing certain neuronal identities. Later, the expression of specific cell surface molecules may direct neurons to extend their axons along the appropriate routes toward their target cells. Thus, nervous system development relies both on characteristic gene expression patterns and on cell-cell interactions.

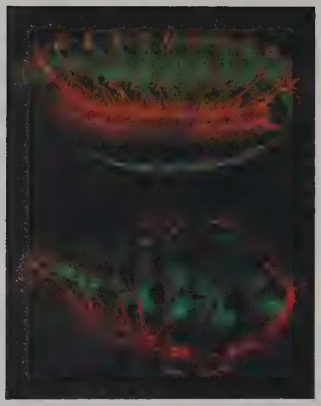
We have developed a general method for directed gene expression in *Drosophila* that allows transcription to be manipulated both spatially and temporally. Through the use of targeted gene expression, transcription patterns in neuronal precursor cells and in their progeny can be altered with the aim of eliciting specific cell fate changes. We have also expressed toxins in a restricted fashion as a means of targeted cell killing. Targeted cell ablation can be used to eliminate the local interactions involved in cell fate determination and in axon guidance.

We are specifically altering gene expression during neurogenesis to investigate the role of segmentation genes in directing neuronal cell fate, and are using targeted cell killing to analyse the role of cell-cell interactions in influencing neuronal identity and in directing axon guidance.

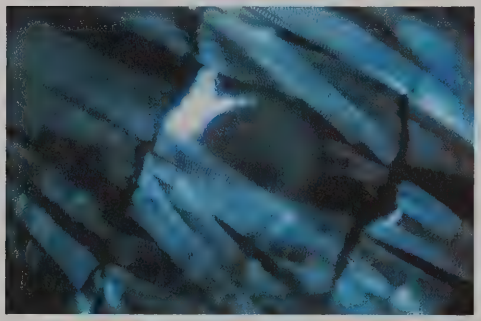
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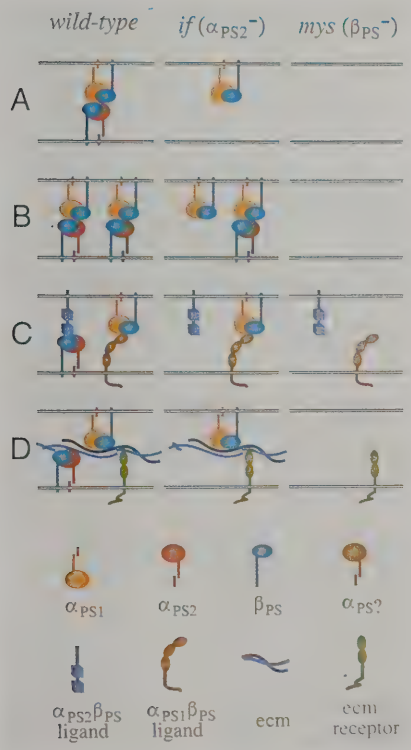


Defects in morphogenesis are found in embryos mutant for the $ß_{PS}$ gene, myospheroid. A normal embryo (top) and one mutant for myospheroid (bottom) are shown stained for the nervous system (red) and the musculature (green)



A weak defect in the muscle structure is caused by an unusual mutation in α_{PS2}, as revealed by polarised light. The muscle in the centre of the picture has detached at one end and contracted.

BROWN, N.H., BLOOR, J.W., DUNIN-BORKOWSKI, O. and MARTIN BERMUDO, M.D. 1993. Integrins and morphogenesis. **Development Suppl.**, 177-183.
BROWN, N.H. 1994. Null mutations in the α_{PS2} and $ß_{PS}$ integrin subunit genes have distinct phenotypes. **Development 120**, 1221-1231.
For further publications see nos.14,15, page 47ff.

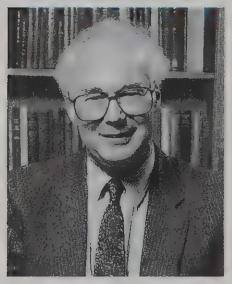


Models of integrin-mediated adhesion. Model A is ruled out since mutations in the α_{PS2} subunit and the β_{PS} subunit have distinct phenotypes, and this model predicts that the phenotypes should be identical. Models B-D are three alternatives which all support the current data, although model D is currently favoured.

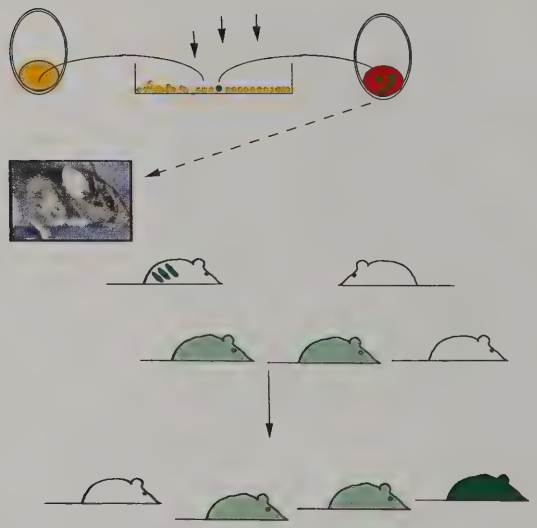
The major interest of our group is to comprehend how an organism is formed through cell interactions during embryogenesis. We are pursuing studies on the structure and function of cell surface proteins that mediate these events, in particular a family of proteins called the integrins. These proteins are involved in a variety of processes involving cell adhesion in humans, including migration of leukocytes to sites of inflammation and the formation of blood clots. In the fruit fly, *Drosophila melanogaster*, the particular integrins that we have identified and characterised appear to mediate adhesion between different tissues (e.g. the adhesion of muscles to the epidermis), judging from the failure of this adhesion to occur in embryos that are mutant for the integrin genes.

We are examining the structure and function of one integrin subunit in detail by generating many different mutations in the gene encoding it, using both classical genetic and site directed approaches, and studying the effect of these changes on the development of the embryo. Our initial results have shown that this integrin has multiple independent functions during development. We are also trying to identify other components of integrin-mediated adhesion by performing genetic screens for new mutations which cause developmental defects similar to those caused by integrin mutations. Finally we are examining whether these integrins transmit signals during normal development.

MARTIN EVANS



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JOANNE WILSON



The route to experimental genetics in the mouse via embryonic stem cells



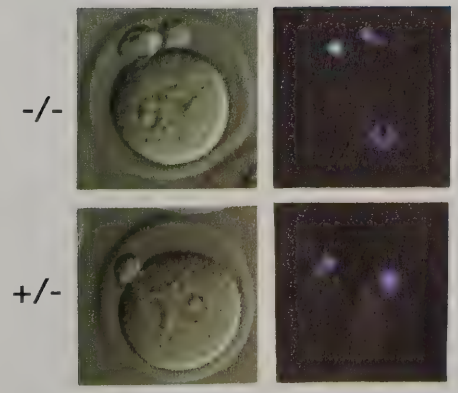
Bulgy eye (Bey) mice either side of a wild-type

COLLEDGE, W.H., CARLTON, M.B.L., UDY, G.B. and EVANS, M.J. 1994. Disruption of *c-mos* causes parthenogenetic development of unfertilized mouse eggs. **Nature 370**, 65-68.

WARREN, A.J., COLLEDGE, W.H., CARLTON, M.B.L., EVANS, M.J., SMITH, A.J.H. and RABBITTS, T.H. 1994. The oncogene cysteine-rich LIM domain protein *rbtn2* is essential for erythroid development. **Cell 78**, 45-57.

For further publications see nos. 21,26,27,31,32,33,79,94,95,96, page 47ff.

MAMMALIAN DEVELOPMENTAL BIOLOGY AND GENETICS THROUGH THE CULTURE OF EMBRYONIC STEM CELLS



The effect of a null mutation of the c-mos locus in mice produced by gene targeting.

The -/- egg proceeds through the second meiotic division spontaneously (2 polar bodies and dividing egg nucleus) whilst the +/- egg which still inherits c-mos in the cytoplasm is normally arrested after the first meiotic division (1 polar body and egg nucleus waiting at the perifery to enter the 2nd meiotic division) (Left panels interference contrast, right fluorescence with DAPI staining.)

The use of embryonic stem (ES) cells of mice as a route to somatic and germ line transgenesis has opened up the route to experimental mammalian genetics. Because these cells provide a bridge between the whole animal and tissue culture, specific genetic modification which may be induced, screened or selected in culture, can be tested and recombined within the context of the physiology and genetics of the whole animal.

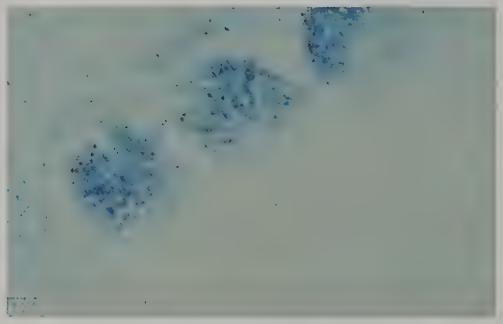
Injection of ES cells into 2.5 day host blastocysts results in chimaeric mice with the ES cells having the ability to contribute to all organs. Germline transmission of the ES cell clone results in multiple transgenic mice which can be analysed to determine the function of transgenes in the development of the mouse.

We are creating a systematic library of mouse mutants resulting from random integration of viral DNA into the genome, and are using homologous recombination to introduce specific mutations into ES cells to study the results of such gene targeting *in vivo* and generate animal models of human diseases. We are concentrating mainly on creating animal models of human disease by specific gene targeting and using retroviral vector mediated insertional mutagenesis.

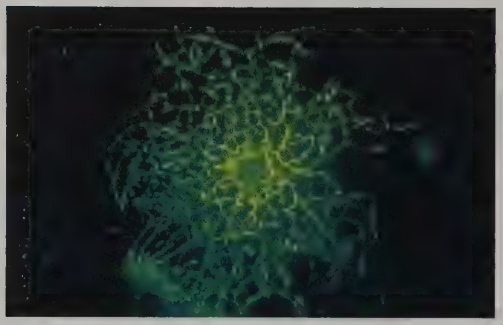
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Fibronectin expression in the developing rat embryo



Oligodendrocyte in cell culture

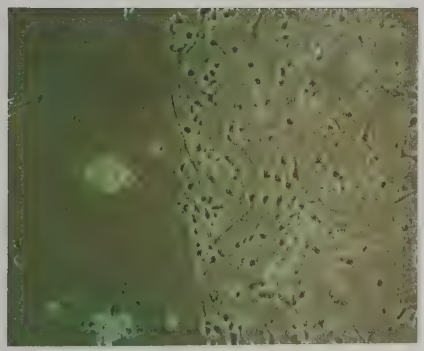
KIERNAN, B.W. and FFRENCH-CONSTANT, C. 1993. Oligodendrocyte precursor (0-2A progenitor cell) migration; a model system for the study of cell migration in the developing CNS. **Development Supplement**, 219-225.

MILNER, R. and FFRENCH-CONSTANT, C. 1994. A developmental analysis of oligodendroglial integrins in primary cells: changes in α v-associated ß subunits during differentiation. **Development 120**, in press

For further publications see nos.24,36,37,38,39,67,68, page 47ff.

DEVELOPMENT AND REPAIR OF THE VERTEBRATE CENTRAL NERVOUS SYSTEM

The focus of our group is the role of cell-extracellular matrix (ECM) interactions in mammalian central nervous system (CNS) development. These interactions have received less attention than the effects of neurotrophins and other growth factors, but evidence from other developmental systems suggests that they will play key roles in controlling cell behaviour. We study the oligodendroglial cells (which form myelin in the mature CNS) as these cells can be identified and manipulated in cell culture.



The repulsive effect of tenascin on rat oligodendrocyte precursors

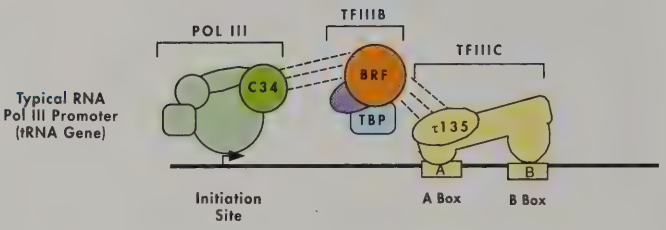
We have shown that different ECM molecules can either stimulate or inhibit oligodendroglial precursor cell migration. We have also shown that the integrins, a major family of cell surface ECM receptors, are regulated during development in a pattern that suggests a role in the control of cell proliferation. We are presently analysing transgenic mice lacking different ECM molecules so as to test directly the roles of these molecules and their receptors.

In addition to these developmental studies we also study repair in the nervous system. Another ECM molecule, fibronectin, appears during peripheral nerve repair and we find that forms of fibronectin produced during early development by alternative splicing of the primary gene transcript are re-expressed during repair. This suggests that efficient repair may require re-use of developmental mechanisms. We hope to use our knowledge of CNS development to devise strategies for repair of the CNS.

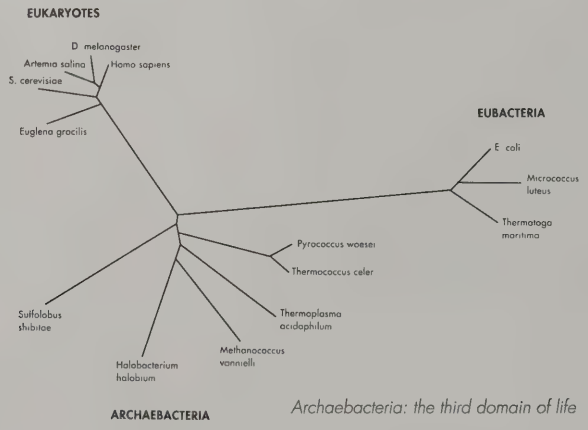
STEVE JACKSON



SIMON BOULTON
DAVID GELL
NICHOLAS FINNIE
TANYA GOTTLIEB
BERNARD KHOO
SOHAIL QURESHI
GRAEME SMITH
ROBERT WHITE



TBP and BRF are central components of the pol III transcriptional apparatus

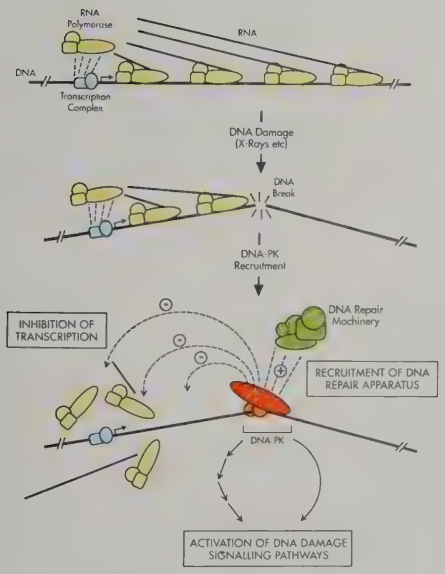


Archaebacteria: the third domain of life

ROWLANDS, T., BAUMANN, P. and JACKSON, S.P. 1994. The TATA-binding protein: a general transcription factor in eukaryotes and archaebacteria. **Science 264**, 1326-1329.

WHITE, R.J., KHOO, B.C-E., INOSTROZA, J.A., REINBERG, D. and JACKSON, S.P. 1994. Differential regulation of RNA polymerases I, II, and III by the TBP-binding repressor Dr1. **Science 266**, 448-450.

For further publications, see nos. 40,41,48,59,93, page 47ff.



Possible functions for DNA-PK at sites of DNA damage

We have discovered that the TATA binding protein (TBP) is an essential subunit of the RNA polymerase III (pol III) general transcription factor TFIIIB. Another pol III transcription factor is BRF. We are currently investigating protein-protein interactions that mediate pol III transcription complex assembly and are defining domains of TBP and BRF involved in this. Recently, we have found that pol III transcription is regulated by the repressor Dr-1 and during the eukaryotic cell cycle.

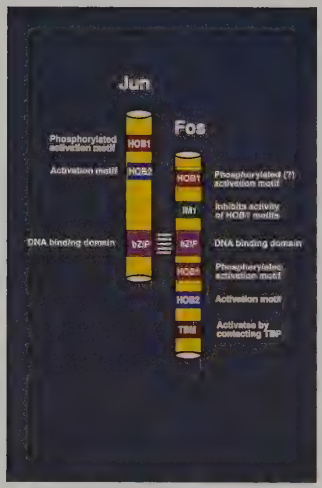
Archaebacteria are a group of organisms distinct from both eukaryotes and eubacteria. Interestingly, we identified TBP and TFIIB/BRF homologues in several archaebacteria and have studied their functions *in vitro*. Our results indicate that the transcriptional machineries of archaebacteria and eukaryotes are fundamentally homologous.

We also study the DNA-dependent protein kinase (DNA-PK), a multiprotein complex comprising human autoimmune antigen Ku and a polypeptide of over 350 kDa (p350). We have cloned the p350 cDNA and are defining important functional domains of this and the Ku subunits. Recently, we have made the striking discovery that mutations in DNA-PK components result in defects in site-specific V(D)J recombination and an inability to repair double-strand DNA breaks induced by ionising radiation. These findings indicate that DNA-PK is a crucial component of the DNA repair/recombination apparatus.

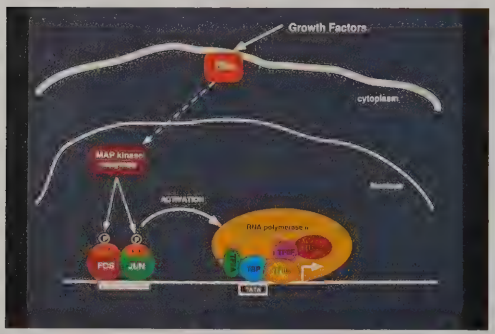
TONY KOUZARIDES



ANDREW BANNISTER
HELEN BROWN
ALISTAIR COOK
PAUL LAVENDER
KLAUS MARTIN
DIDIER TROUCHE



c-Fos and c-Jun sequence motifs and their function



c-Fos and c-Jun have a motif (HOB1) which is phosphorylated by MAP kinase-like enzymes in response to Ras

METZ, R., BANNISTER, A.J., SUTHERLAND, J.A., HAGEMEIER, C., O'ROURKE, E.C., COOK, A., BRAVO, R. and KOUZARIDES, T. 1994. C-Fos-induced activation of a TATA-box-containing promoter involves direct contact with TATA-box-binding protein. **Mol. Cell. Biol. 14**, 6021-6029.

HAGEMEIER, C., CASWELL, R., HAYHURST, G., SINCLAIR, J. and KOUZARIDES, T. 1994. Functional interaction between the HCMV IE2 transactivator and the retinoblastoma protein. **EMBO J. 13**, 2897-2903.

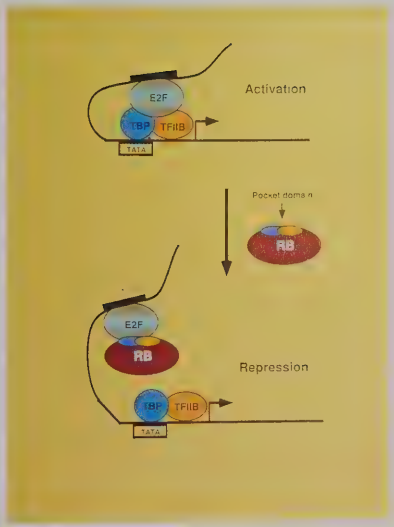
For further publications see nos. 9,13,19,43,74,100, page 47ff.

TRANSCRIPTIONAL REGULATION IN EUKARYOTES

Our group is interested in defining the mechanisms by which regulatory transcription factors modulate gene expression and how these functions correlate with oncogenic transformation. We are currently concentrating on two oncogenic transcription factors, c-Fos and c-Jun, and a transcriptional repressor, the Retinoblastoma tumour suppressor protein.

Our analysis of c-Fos and c-Jun indicates that they possess a homologous activation domain containing two motifs, HOB1 and HOB2. The activity of the HOB1 motif is regulated by Ras-induced phosphorylation and is silenced by an inhibitor motif (IM1) present within c-Fos. We have shown that c-Fos and a related protein, FosB, can activate transcription by containing TBP. Interaction between FosB and TBP is required for FosB-induced oncogenic transformation.

The Retinoblastoma protein (RB) can bind to the E2F transcription factor and silence its ability to activate transcription. We have shown that RB has extensive sequence similarity to TBP and a second general transcription factor TFIIB. This has led us to propose that RB represses E2F by preventing it from binding TBP and TFIIB. Recently we have found that the function of RB is regulated by a viral transcription factor, IE2, expressed by the human cytomegalovirus (HCMV).



Model for RB-induced repression of E2F: the RB pocket domain, which has homology to TBP and TFIIB, prevents E2F from contacting TBP and TFIIB.

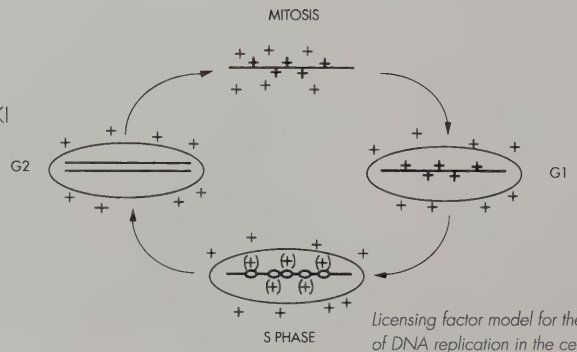
RON LASKEY



DAWN COVERLEY
COLIN DINGWALL
DIRK GÖRLICH
CHONG YEE KHOO
TORSTEN KRUDE
MARK MADINE
JOE MAKKERH
JACKIE MARR
TONY MILLS
HANNAH PEEL
PIOTR ROMANOWSKI



Importin is essential for the first step of nuclear protein import, namely binding to the nuclear envelope



Licensing factor model for the control of DNA replication in the cell cycle

COVERLEY, D., DOWNES, C.S., ROMANOWSKI, P. and LASKEY, R.A. 1993. Reversible effects of nuclear membrane permeabilization: evidence for a positive licensing factor. **J. Cell Biol. 122**, 985-992.

GÖRLICH, D., PREHN, S., LASKEY, R.A. and HARTMANN, E. 1994. Isolation of a protein that is essential for the first step of nuclear protein import. **Cell**, in press.

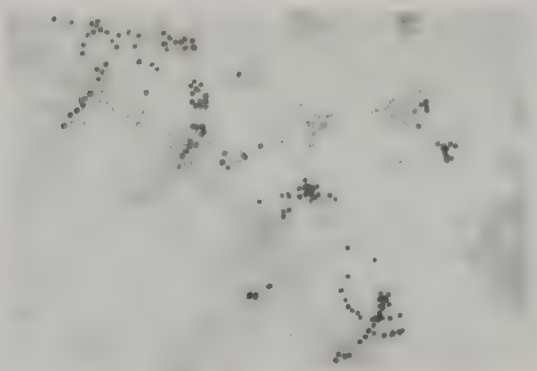
For further publications see nos. 25;30,62,63,64,87, page 47ff.

CONTROL OF EUKARYOTIC CHROMOSOME REPLICATION AND NUCLEAR PROTEIN IMPORT

We are analysing the control of eukaryotic chromosome replication using cell-free systems derived from eggs of *Xenopus laevis*.

Replication is coupled to the cell cycle so that DNA replicates only once between consecutive divisions. Disrupting the nuclear membrane overcomes this mechanism allowing a further cycle of complete replication. This observation can be explained by the licensing factor model of Blow and Laskey shown opposite. We have found that the replication capacity of nuclei from synchronised human cells can be accounted for by a similar model. Membrane repair experiments have demonstrated the existence of a factor with these properties and provided an assay for its isolation. In parallel we are investigating a family of known proteins, the mcm3 family, which show striking similarities to the predicted behaviour of licensing factor.

We are also investigating how nuclear proteins are targeted to the cell nucleus. We have identified a bipartite class of nuclear targeting sequence which appears to be common in nuclear proteins and have now identified a protein, importin, which performs the initial membrane binding step of nuclear protein import. We are investigating proteins and mechanisms involved in nuclear protein transport.

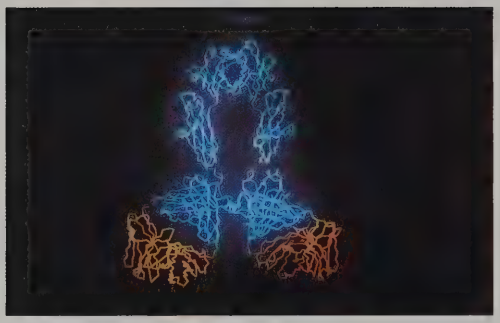


Nuclear proteins (coated on gold particles) bind to fibrils outside the nuclear pore complex before passing through the centre of the pore

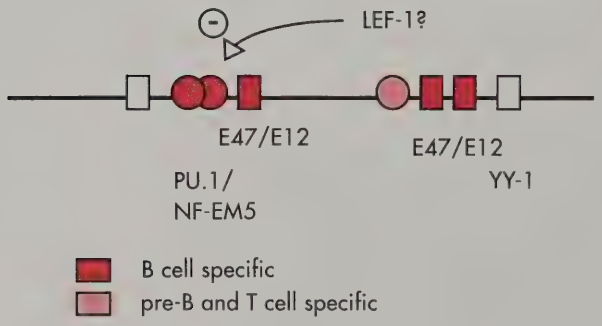
KERSTIN MEYER



JOHN IRELAND



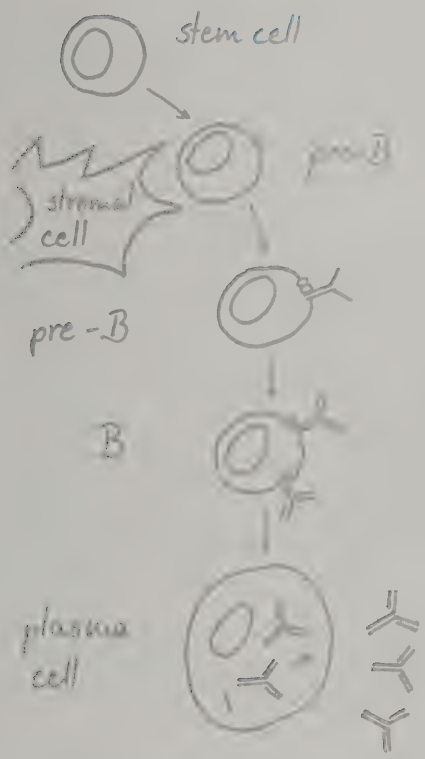
Structure of an Ig molecule with the variable regions shown in red



Summary of factors known to bind the κ3′ enhancer

MEYER, K.B. and IRELAND, J. 1994. Activation of the immunoglobulin κ3′ enhancer in pre-B cells correlates with the suppression of a nuclear factor binding to a sequence flanking the active core. **Nucleic Acids Res. 22**, 1576-1582.

COOK, G.P., MEYER, K.B., NEUBERGER, M.S. and PETTERSSON, S. 1995. Regulated activity of the IgH intron enhancer (Eμ) in the T-lymphocyte lineage. **Internat. Immunol.**, in press.



Schematic representation of B cell development

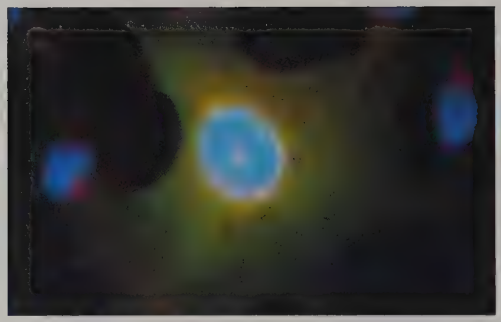
During the development of a mature B cell from a haematopoietic stem cell, immunoglobulin (Ig) genes undergo a complex pattern of gene rearrangement and subsequent expression. Our work focuses on the activation of the Igκ gene at the developmental switch from a pre-B to a B cell. In pre-B cells the activity of the κ3′ enhancer, which was described in our previous work, is silenced by a region flanking an active core element. We have now identified a lymphoid specific nuclear factor that binds to a site within this repressor region. Developmental studies of this factor show a pattern of expression consistent with a role as a transcriptional repressor of the Igκ enhancer. By several criteria this factor is identical to LEF-1 and we are currently investigating whether LEF-1 acts as developmental switch for κ3′ enhancer function.

In addition, we are studying the involvement of HLH (helix-loop-helix) proteins in the control of Ig gene expression. The formation of either homo- or heterodimers is known to control their ability to activate transcription during very early stages of B cell development. We have now shown that a dominant negative HLH factor, Id3, is expressed in B cells but not in plasma cells. Id3 is able to downregulate IgH3′enhancer activity in transfection studies and is thus likely to be an important modulator of Ig gene expression.

JONATHON PINES



MALCOLM FIRTH
MARK JACKMAN
EMMA KELLY
ANNA MEDDINS



Cell stained with anti-cyclin B1 (green) Höchst 33342 (blue) and wheatgerm agglutinin (red)

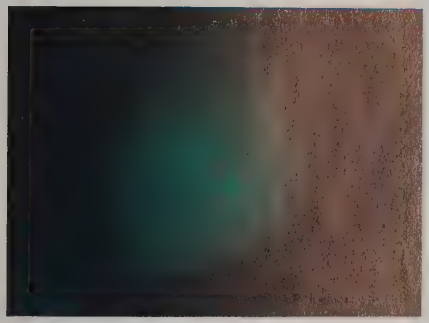


Cell stained with anti-cyclin B2 (red)

Cyclin B1 and B2 localised to different sub-cellular structures. It is clear that cyclin B1 binds to microtubules and cyclin B2 localises to the golgi and vesicle compartment

PINES, J. and HUNTER, T. 1991. Human cyclins A and B are differentially located in the cell and undergo cell cycle dependent nuclear transport. **J. Cell Biol. 115**, 1-17.
PINES, J. and HUNTER, T. 1994. The differential localisation of human cyclins A and B is due to a cytoplasmic retention region in cyclin B. **EMBO. J. 13**, 3772-3781.
For further publications see nos. 55;81,82,83, page 47ff.

REGULATION OF THE MAMMALIAN CELL CYCLE BY CYCLIN-DEPENDENT KINASES



Cell stained with anti-cyclin B1 antibodies



Same cell stained with anti-tubulin antibodies

Cyclin B1 binds to the mitotic apparatus

Dividing cells ensure that DNA replication and cell division are sequential by a regulated series of steps called the cell cycle. Critical steps in the cell cycle are regulated by the cyclin-dependent kinases (CDKs). Cyclins activate and localise each CDK to the correct sub-cellular structures.

We are studying how cyclins localise CDKs to particular parts of the cell. We have shown that cyclin A is a nuclear protein, and associated with a transcription factor complex. By contrast, cyclins B1 and B2 are cytoplasmic throughout interphase. Cyclin B1 is associated with microtubules, whereas cyclin B2 localises to the Golgi apparatus. At mitosis, cyclin B1 binds to the spindle whereas cyclin B2 remains associated with vesicles. The B-type cyclin-cdc2 complexes are only active in mitosis, suggesting that cyclin B1-cdc2 is responsible for re-organising the cytoskeleton, and cyclin B2-cdc2 for disassembling the Golgi and ER.

Our research focuses on defining which parts of the cyclins are responsible for their location. We are using chimeric proteins and point mutants to pin-point the regions of the cyclins responsible for their targeting. We are searching for proteins that are able to interact specifically with different cyclins using the yeast 2 hybrid screen, and are looking for substrates that are specific to each type of cyclin.

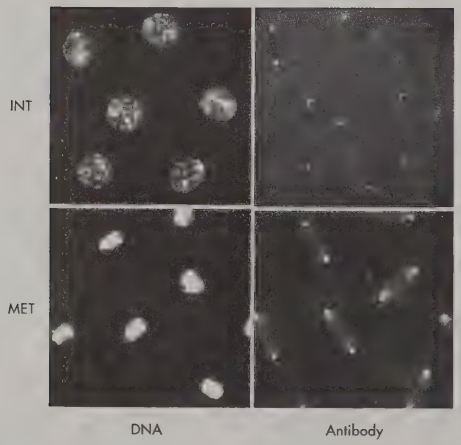
JORDAN RAFF



DEBORAH KIDD



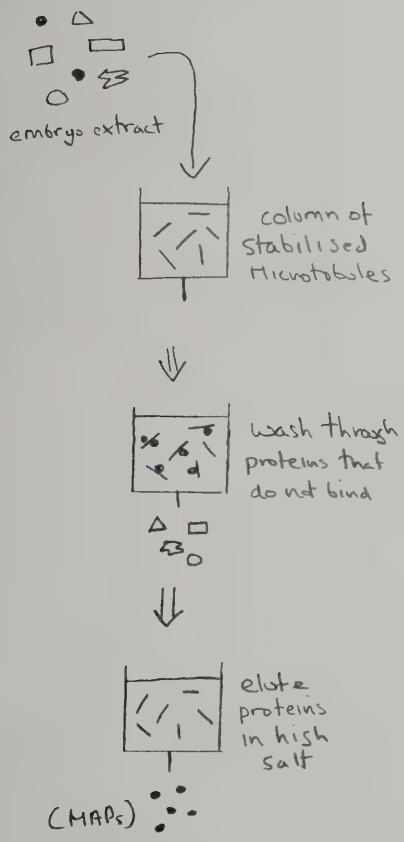
Centrosomes (blue) and chromosomes (red) during anaphase in an early Drosophila *embryo.*



The localisation of the LK6 protein kinase to centrosomes in interphase (INT) and metaphase (MET)

GLOVER, D.M., GONZALEZ, C. and RAFF, J.W. 1993. The centrosome. **Scientific American 268**, 62-68.

RAFF, J.W., KELLOGG, D.R. and ALBERTS, B.M. 1993. *Drosophila* γ-tubulin is part of a complex containing two previously identified centrosomal MAPs. **J. Cell Biol. 121**, 823-825.



Microtubule column affinity chromatography

The centrosome is the main microtubule organising centre in animal cells. This organelle plays a crucial role in many aspects of cellular organisation, yet very little is known about its structure or how it functions. Using the early *Drosophila* embryo as a model system, we have begun a molecular dissection of the centrosome by isolating a number of proteins that bind to microtubules *in vitro* and are located in the centrosome *in vivo*. Using antibodies raised against these proteins we have cloned cDNAs that encode four of them.

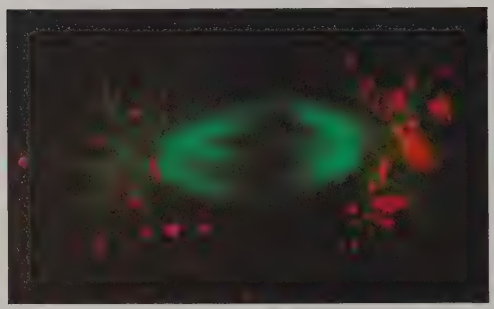
Two of these proteins, called DMAP190 and DMAP60, bind directly to each other and to microtubules. Both proteins are components of a larger protein complex that includes γ-tubulin, a highly conserved centrosomal protein that is thought to be involved in the interaction between centrosomes and microtubules. Another is a protein kinase - the first protein kinase shown to be located in the centrosome and to interact with microtubules. Phosphorylation events are known to regulate the microtubule nucleating properties of centrosomes, and this protein is an excellent candidate for a protein involved in this process. Interestingly, the kinase phosphorylates DMAP60 *in vitro*.

We are using a variety of molecular, biochemical, cell biological, and genetic approaches to study the functions of these centrosomal proteins and to isolate new proteins that associate with them.

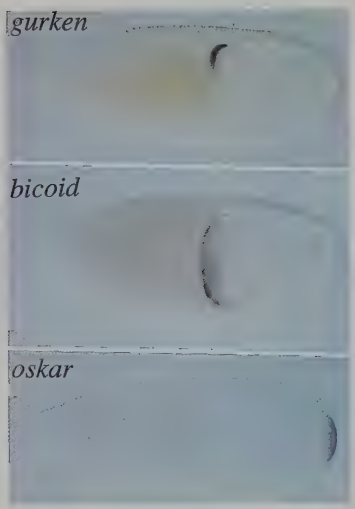
DANIEL ST JOHNSTON



HEATHER ELLIOT
ACAIMO GONZÁLEZ-REYES
STEFAN GRÜNERT
DAVID MICKLEM
MATTHEW WESTON
CHIHIRO YAMADA



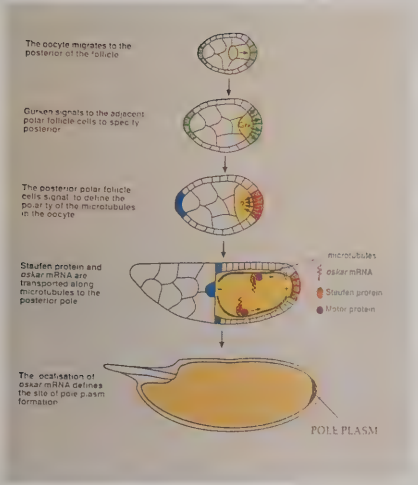
Staufen protein (red) associates with injected bicoid RNA to form particles which migrate to the poles of the mitotic spindles (green)



The localisation of gurken, bicoid *and* oskar *mRNAs to three distinct positions within the* Drosophila *oocyte. The accumulation of* gurken *mRNA in the dorsal/anterior corner of the oocyte establishes dorsal-ventral polarity, while the localisation of* bicoid *and* oskar *mRNAs to opposite poles determines the anterior-posterior axis.*

ST JOHNSTON, D. 1993. Pole plasm and the posterior group genes. *In*: **The Development of *Drosophila*** (M. Bate & A. Martinez-Arias Eds), Cold Spring Harbor Press, New York, 325-363.
GONZÁLEZ-REYES, A. and ST JOHNSTON, D. 1994. The role of oocyte position in the establishment of anterior-posterior polarity in *Drosophila*. **Science 266**, 639-642.
For further publications see nos.35,88,89, page 47ff.

mRNA LOCALISATION AND THE ORIGIN OF POLARITY IN THE *DROSOPHILA* EGG



The steps in the specification of the posterior pole of the egg.

The primary axes of many organisms are defined by localised cytoplasmic determinants in the egg. These signals have been best characterized in *Drosophila*, where the localisation of *bicoid*, *oskar* and *gurken* mRNAs determines the polarity of both the anterior-posterior and the dorsal-ventral axes. We are taking several approaches to investigate how these mRNAs are transported within the oocyte, with a view to understanding both the basic mechanisms of mRNA localisation, and the origins of polarity.

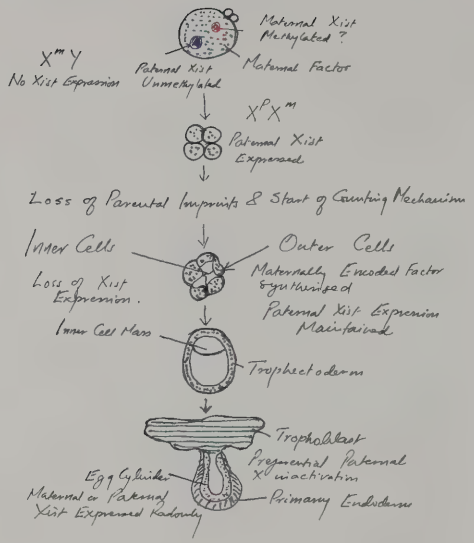
1) The maternal gene *staufen* is required for both the anchoring of *bicoid* mRNA at the anterior pole of the egg, and for the transport of *oskar* mRNA to the posterior pole. Staufen protein associates with each transcript during its localisation, and contains several copies of a novel double-stranded RNA- binding domain. Using a combination of genetic and biochemical approaches, we are investigating how this protein recognises two different mRNAs, and what role it plays in their transport. Several experiments are also under way to identify other components of the transport machinery, in particular the microtubule motor that transports Staufen when it is associated with the appropriate mRNA.

2) The localisation of *oskar* mRNA depends upon a pre-existing anterior-posterior polarity within the oocyte. We have recently found that this asymmetry originates from the movement of the oocyte to the posterior of the egg chamber, and we are now studying the genetic control of this process.

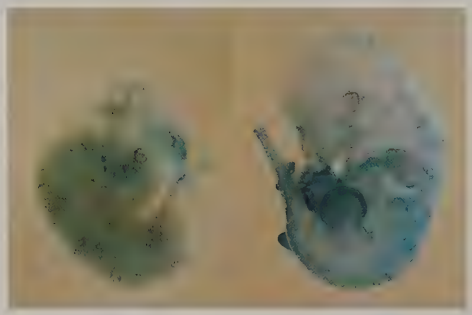
AZIM SURANI



JUSTIN AINSCOUGH
SHEILA BARTON
JAMES BRENTON
KATHY HILTON
NOBUAKI KIKYO
TSUYOSHI KOIDE
LOUIS LEFEBVRE
LI-LAN LI
MAITHREYI NARASIMHA
WILLIAM RIDEOUT III
FAY SHAMANSKI
MASAKO TADA
TAKASHI TADA
STÉPHANE VIVILLE



Xist expression in early mouse development



The distribution of gynogenetic and androgenetic cells in chimeras using ß galactosidase as an in situ *marker.*

KAY, G.F., BARTON, S.C., SURANI, M.A. and RASTAN, S. 1994. Imprinting and X chromosome counting mechanisms determine *Xist* expression in early mouse development. **Cell 77**, 171-182.

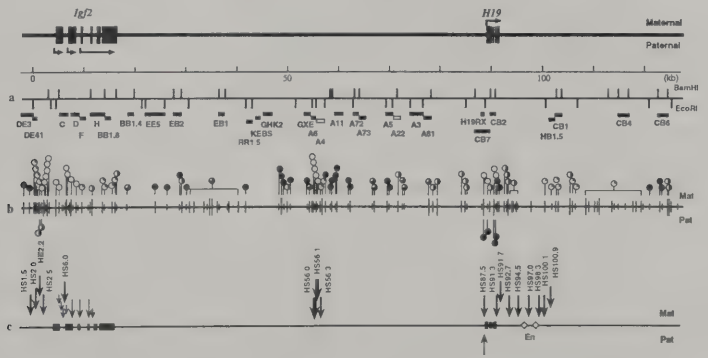
ALLEN, N.D., BARTON, S.C., HILTON, K., NORRIS, M.L. and SURANI, M.A. 1994. A functional analysis of imprinting in parthenogenetic embryonic stem cells. **Development 120**, 1473-1482.

For further publications see nos. 6,22,34,42,61,78,80,91,92,97, page 47ff.

Development in the mouse requires both a maternal and a paternal genome because expression of imprinted genes is determined by their parental origin. The transcriptional control of expression of the appropriate parental allele is determined by germline-specific heritable epigenetic modifications of DNA or chromatin structure.

A long range physical analysis of the distal region of chromosome 7 identified DNA methylation and chromatin structural differences between the parental alleles of reciprocally imprinted *Igf-2* and *H19* genes, together with an intergenic region that may contain an important regulatory element. Analysis of the *Xist* gene showed expression of the paternal gene in pre-implantation embryos; these imprints are apparently erased and an X chromosome counting mechanism imposes an appropriate control over *Xist* expression that may involve a product of a novel maternally expressed gene. The combined studies illustrate how large domains and individual loci within them are molecularly marked for parental imprinting.

The effects of imprinted genes on development have been examined in androgenetic (AG: duplicated paternal genome) and gynogenetic (GG: duplicated maternal genome) embryos and embryonic stem cells. In chimeras as well as in ectopic sites, androgenetic cells differentiate into mesodermal tissues including skeletal muscle and cartilage and gynogenetic cells into surface ectoderm and neural tissues. With the identification of further imprinted genes, the effects of individual genes on development can be assessed in gain and loss of function transgenic mice.

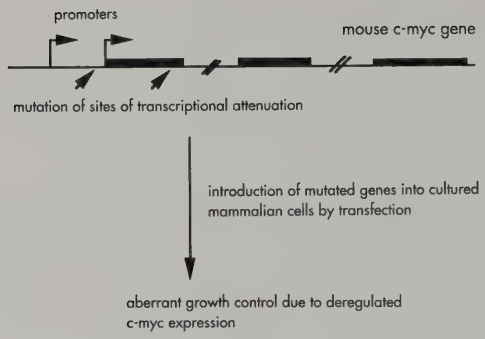


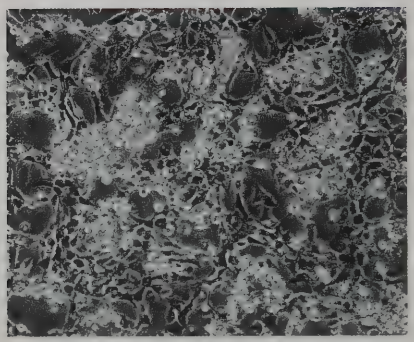
Long-range physical analysis of an imprinted domain with the reciprocally imprinted Igf-2 *and* H19 *genes.*

STEPHANIE WRIGHT



CRAIG LUCCARINI



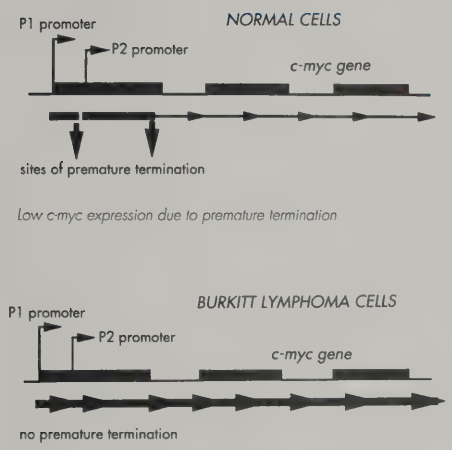


Cells transformed by over expression of the c-myc oncogene

WRIGHT, S. 1993. Regulation of eukaryotic gene expression by transcriptional attenuation. **Mol. Biol. of the Cell 4**, 661-668.

WRIGHT, S., LU, X. and PETERLIN, B.M. 1994. Human immunodeficiency virus type 1 Tat directs transcription through attenuation sites within the mouse c-myc gene. **J. Mol. Biol. 243**, 568-573.

REGULATION OF PROTO-ONCOGENE EXPRESSION IN NORMAL AND TUMOUR CELLS



Transcription through the c-myc gene in normal and tumour cells

The development of neoplasia is often a result of the aberrant expression of genes that normally act to control cellular proliferation and differentiation. The aim of our work is to determine the mechanism whereby transcriptional attenuation is used to regulate expression of three such genes (c-myc, c- fos and c-myb) in normal cells, and to characterise the events leading to the loss of ability to regulate attenuation within the c-myc gene in a variety of tumours.

We have previously shown that the c-myc, c-fos and c-myb genes are normally regulated via the modulation of transcriptional elongation through discrete sites of premature termination within the gene, with the degree of transcriptional attenuation being controlled in response to different physiological signals. We have characterised common sequence elements and factors interactions at sites of premature termination within these genes, and have analysed the *regulatory* elements that enable the *degree* of attenuation within different genes to be independently controlled.

We are currently determining whether aberrant regulation of transcriptional attenuation within the c-myc gene in tumours is due to alterations in protein interactions at such regulatory elements.

ANNE McLAREN



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GERM CELLS IN THE MOUSE EMBRYO

Embryonic germ cells, the cells whose descendants give rise to eggs in the female, sperm in the male, move from the extra-embryonic region where they are located during gastrulation, to the genital ridges, the site of the future gonads.

For part of their journey, they appear to be migrating actively. During this period, we have shown that most of the germ cells are linked by cell processes into a network, rather than migrating singly. At present we are exploring the role that cell-cell adhesion molecules and extracellular matrix molecules play in the migration of these cells.

Once in the genital ridges, germ cells in female embryos enter meiotic prophase and develop as oocytes. In male embryos, on the other hand, the germ cells stop dividing until after birth. The first spermatogenic cells do not enter meiosis until a week after birth. By mixing and explantation experiments, we are attempting to identify the somatic signals that direct germ cells into either oogenesis or spermatogenesis.



Germ cells (green) emigrating from the hind gut. Contact with laminin (red) seems unavoidable.

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For further publications see nos.16,17;44,69,70,72,73, page 47ff.

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As part of the University of Cambridge, the Institute welcomes enquiries from prospective graduate students. We have a thriving population of graduates who contribute greatly, not only to the stimulating research environment, but also to the life of the Institute as a whole. Additionally, graduates become members of a Biological or Medical Sciences Department with which their group leader is affiliated.

Graduate studentships are supported mainly by the Wellcome Trust or the Cancer Research Campaign but additional sponsorship may be applied for from a variety of sources, including the Government Research Councils.

Applicants should write, in the first instance, to the leader of the group whose work interests them.

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OTHER ACTIVITIES

MICHAEL AKAM is a member of the Wellcome Cell & Molecular Biology Board.

MARTIN EVANS is Chairman of the AFRC Stem Cell & Molecular Biology Working Party, Founder and Director of Genesys Instruments Ltd, Founder Member of Animal Biotechnology, Cambridge Ltd.

JOHN GURDON is currently a member of the Councils of the Royal Society and the Cancer Research Campaign, and is a Governor of the Wellcome Trust.

RON LASKEY is Subject Convenor for Cell and Developmental Biology, Academia Europaea, a member of the Cancer Research Campaign Scientific Committee, and a Trustee and Chairman of the Board of the Management Committee of Strangeways Research Laboratories.

DANIEL ST JOHNSTON has been invited by the Genetical Society to give the 1995 Balfour Lecture. This lectureship recognises the contribution of an outstanding geneticist under the age of 36.

MEMBERS OF STAFF ON THE EDITORIAL BOARDS OF JOURNALS:

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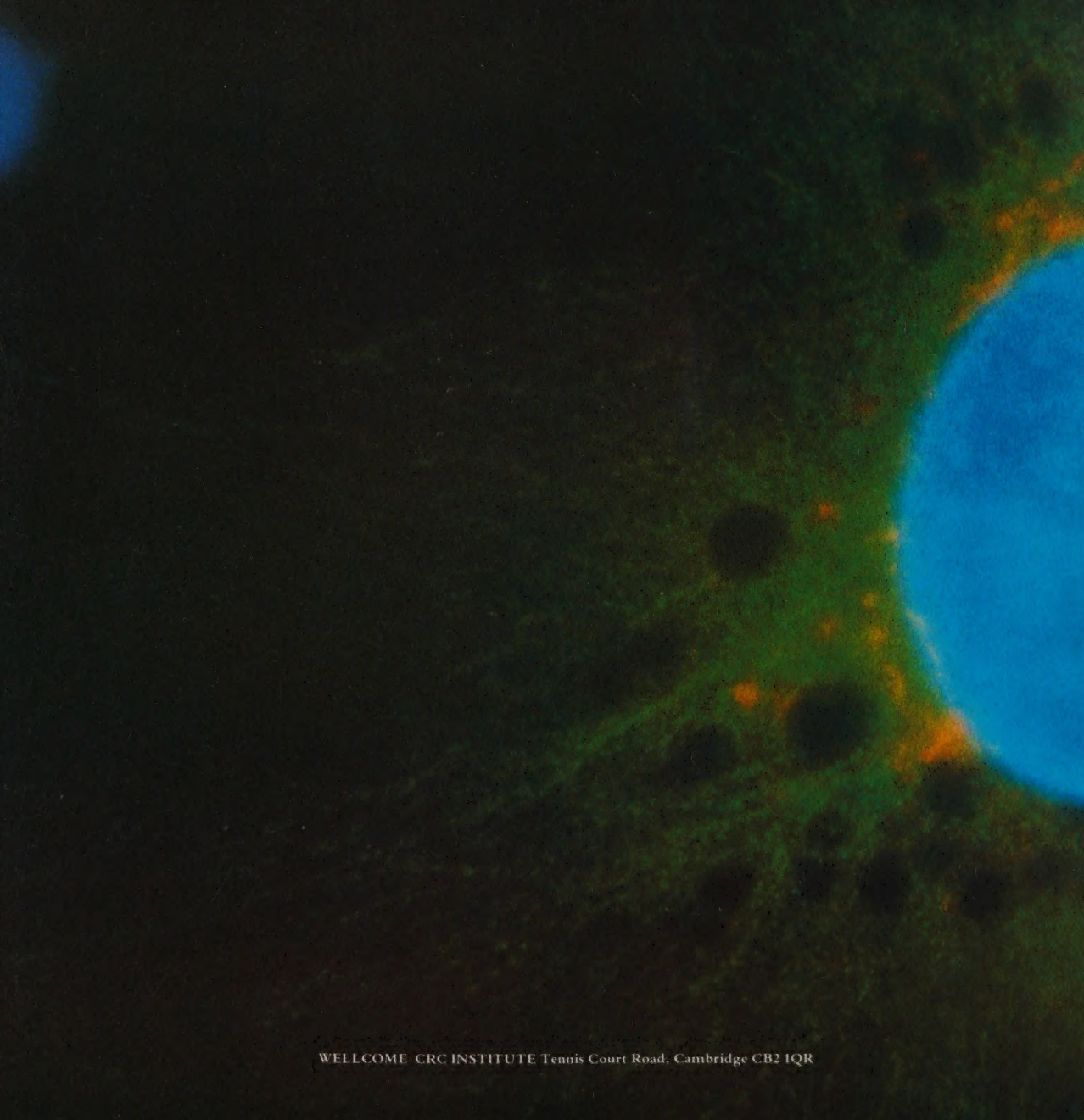
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